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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/050,189 | 01/16/2002 | Berish Rubin | Rubin-201-KGB | 6280 |

7590 10/01/2007

Peter I. Bernstein
Scully, Scott, Murphy & Presser
400 Garden City Plaza
Garden City, NY 11530

| EXAMINER | |
|---|---|
| MYERS, CARLA J | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1634 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 10/01/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/050,189 | RUBIN ET AL. | |
| | Examiner | Art Unit | |
| | Carla Myers | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *3-8 and 13-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-8 and 13-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. This action is in response to the amendment filed July 3, 2007. Applicant's arguments regarding the 102(e) rejection of claims 3-6 and 14-17 over Slaugenhaupt (US 2002/0169299) and the 103 rejection over claims 7 and 8 over Slaugenhaupt (US 2002/0169299) are convincing regarding the fact that '299 application no longer includes claims directed to methods for detecting a polymorphism associated with familial dysautonomia. Accordingly, these rejections over Slaugenhaupt (US 2002/0169299) are withdrawn in favor of new grounds of rejection over Slaugenhaupt (US 2005/0204409) as set forth below.

2. Claims 3-8 and 13-17 are pending and have been examined herein. This action is made non-final.

### New Grounds of Rejection

### Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 3-6 and 14-17 are rejected under 35 U.S.C. 102(e) as being anticipated by Slaugenhaupt (US 2005/0204409).

Slaugenhaupt (pages 10-12) teaches methods for detecting the presence of a mutation in the IKAP gene (referred to therein as the "IKBKAP" gene). In particular, Slaugenhaupt teaches methods which detect the presence of the T to C substitution at position 6 in the donor splice site of intron 20 and methods which detect the presence of a G to C transversion in exon 19, which results in an arginine to proline substitution at amino acid position 696 (referred to therein as nucleotide position 2397; see page 1, column 2). Slaugenhaupt teaches that the presence of each of these mutations is associated with the occurrence of FD (page 11). With respect to claims 5 and 6, Slaugenhaupt teaches that the nucleic acid to be analyzed is obtained by PCR amplification (page 4, column 2) and that the mutation may be detected by SSCP analysis (page 5, column 2). Accordingly, the method of Slaugenhaupt anticipates the claimed invention.

**Response to Remarks / Declaration:**

In the response, Applicants cite MPEP 2305 as stating that a 131 declaration may be used to overcome a reference unless that reference is a patent or application published under 35 USC 122(b) and the reference has claims directed to the same patentable invention as the application claims are being rejected. Applicants state that the Examiner has not established that the '299 publication and the present application are directed to the same patentable invention. The examiner agrees that the '299 publication is not directed to the same invention as set forth in rejected claims 3-6 and 14-17. Accordingly, the rejection of claims 3-6 and 14-17 over the '299 publication is withdrawn.

However, as set forth above, the rejection is now made over Slaugenhaupt (US 2005/0204409). The '409 publication discloses and claims the same invention as that of present claims 3-6 and 14-17. Thereby, since Slaugenhaupt (US 2005/0204409) includes claims directed to the same patentable invention as the application claims being rejected, a declaration under 37 CFR 1.131 may not be relied upon to overcome the Slaugenhaupt reference.

Applicants assert that the claims corresponding to the '299 publication are not allowable. Applicants also note that a divisional of the '299 publication has been filed and that the claims in the divisional application are not allowable. Applicants conclude that the 131 Declaration should be considered proper to antedate the '299 application.

However, as set forth above, the rejection is now made over the Slaugenhaupt (US 2005/0204409) publication, which does claim the same invention as that of the present application. Again, an affidavit or declaration is inappropriate under 37 CFR 1.131(a) when the reference is claiming the same patentable invention, see MPEP § 2306. If the reference and this application are not commonly owned, **the reference can only be overcome by establishing priority of invention through interference proceedings.**

Regarding interference proceedings, Applicants attention is directed to MPEP 2304.02 and 37 CFR 41.202, set forth in part below:

**37 § 41.202 Suggesting an interference.**
(a) Applicant . An applicant, including a reissue applicant, may suggest an interference with another application or a patent. The suggestion must:
(1) Provide sufficient information to identify the application or patent with which the applicant seeks an interference,

(2) Identify all claims the applicant believes interfere, propose one or more counts, and show how the claims correspond to one or more counts,
(3) For each count, provide a claim chart comparing at least one claim of each party corresponding to the count and show why the claims interfere within the meaning of § 41.203(a),
(4) Explain in detail why the applicant will prevail on priority,
(5) If a claim has been added or amended to provoke an interference, provide a claim chart showing the written description for each claim in the applicant's specification, and
(6) For each constructive reduction to practice for which the applicant wishes to be accorded benefit, provide a chart showing where the disclosure provides a constructive reduction to practice within the scope of the interfering subject matter.
(b) Patentee . A patentee cannot suggest an interference under this section but may, to the extent permitted under § 1.99 and § 1.291 of this title, alert the examiner of an application claiming interfering subject matter to the possibility of an interference.
(c) Examiner . An examiner may require an applicant to add a claim to provoke an interference. Failure to satisfy the requirement within a period (not less than one month) the examiner sets will operate as a concession of priority for the subject matter of the claim. If the interference would be with a patent, the applicant must also comply with paragraphs (a)(2) through (a)(6) of this section. The claim the examiner proposes to have added must, apart from the question of priority under 35 U.S.C. 102 (g):
(1) Be patentable to the applicant, and
(2) Be drawn to patentable subject matter claimed by another applicant or patentee.
(d) Requirement to show priority under 35 U.S.C. 102(g) .(1) When an applicant has an earliest constructive reduction to practice that is later than the apparent earliest constructive reduction to practice for a patent or published application claiming interfering subject matter, the applicant must show why it would prevail on priority.
(2) If an applicant fails to show priority under paragraph (d)(1) of this section, an administrative patent judge may nevertheless declare an interference to place the applicant under an order to show cause why judgment should not be entered against the applicant on priority. New evidence in support of priority will not be admitted except on a showing of good cause. The Board may authorize the filing of motions to redefine the interfering subject matter or to change the benefit accorded to the parties.
(e) Sufficiency of showing . (1) A showing of priority under this section is not sufficient unless it would, if unrebutted, support a determination of priority in favor of the party making the showing.
(2) When testimony or production necessary to show priority is not available without authorization under § 41.150(c) or § 41.156(a), the showing shall

include:
(i) Any necessary interrogatory, request for admission, request for production, or deposition request, and
(ii) A detailed proffer of what the response to the interrogatory or request would be expected to be and an explanation of the relevance of the response to the question of priority.

**Claim Rejections - 35 USC § 103**

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Slaugenhaupt (US 2005/0204409).

Slaugenhaupt (pages 10-12) teaches methods for detecting the presence of a mutation in the IKAP gene (referred to therein as the "IKBKAP" gene). In particular, Slaugenhaupt teaches methods which detect the presence of the T to C substitution at position 6 in the donor splice site of intron 20 and methods which detect the presence of a G to C transversion in exon 19, which results in an arginine to proline substitution at amino acid position 696 (referred to therein as nucleotide position 2397; see page 1, column 2). Slaugenhaupt teaches that the presence of each of these mutations is associated with the occurrence of FD (page 11). The reference also teaches that the nucleic acid to be analyzed is obtained by PCR amplification (page 4, column 2). Slaugenhaupt exemplifies primers for amplifying nucleic acids to detect the T to C substitution at position 6 in the donor splice site of intron 20 and the G to C transversion

in exon 19 (see page 12, col. 1). Slaugenhaupt does not exemplify primers consisting of the sequences of presently claimed SEQ ID NO: 6-9.

However, Slaugenhaupt does teach the genomic sequence of the IKAP gene (see Figure 6 therein) and teaches that the cDNA for this sequence was known in the art at the time the invention was made (see page 10). Given the disclosure of Slaugenhaupt of the location of the 2 mutations within the IKAP gene, the disclosure of the genomic and cDNA sequences flanking the 2 mutations, and the disclosure of the use of PCR primers to amplify nucleic acid sequences containing the 2 mutations, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have generated additional primers, including the primers of present SEQ ID NO: 6-9, in order to have facilitated the detection of the intron 20 splice site and exon 19 mutations. Designing primers which are equivalents to those taught in the art is routine experimentation. The parameters and objectives involved in the selection of primers were well known in the art at the time the invention was made. Moreover, software programs were readily available which aid in the identification of conserved and variable sequences and in the selection of optimum primer pairs. The prior art is replete with guidance and information necessary to permit the ordinary artisan to design additional primers for the amplification of IKAP sequences containing the FD associated mutations in the intron 20 splice site and exon 19. As discussed above, the ordinary artisan would have been motivated to have designed additional primers for amplifying IKAP sequences so as to have provided additional primers which could be used to amplify and detect the FD mutations in the intron 20 splice site and exon 19. Further, the

ordinary artisan would have had more than a reasonable expectation of success of obtaining additional primers for amplifying IKAP sequences. Thus, for the reasons provided above, and in the absence of evidence to the contrary, the primers of present SEQ ID NO: 6-9 and the use of these primers in methods for detecting the FD mutations in intron 20 and exon 19 would have been obvious to one of ordinary skill in the art.

**Response to remarks:**

In the response, Applicants state that the rejection based on the '299 application as the primary reference can no longer stand. However, as set forth above, the rejection is now made with respect to Slaugenhaupt (US 2005/0204409). Further, the response to Applicant's arguments set forth in paragraph 3 above apply equally to the present grounds of rejection.

5. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Slaugenhaupt (US 2002/0169299) in view of Ahren (The Scientist. July 1995. 19 (155): 20-24).

Slaugenhaupt (pages 10-12) teaches methods for detecting the presence of a mutation in the IKAP gene (referred to therein as the "IKBKAP" gene). In particular, Slaugenhaupt teaches methods which detect the presence of the T to C substitution at position 6 in the donor splice site of intron 20 and methods which detect the presence of a G to C transversion in exon 19, which results in an arginine to proline substitution at amino acid position 696 (referred to therein as nucleotide position 2397; see page 1, column 2). Slaugenhaupt teaches that the presence of each of these mutations is associated with the occurrence of FD (page 11). The reference also teaches that the

nucleic acid to be analyzed is obtained by PCR amplification (page 4, column 2). Slaugenhaupt exemplifies primers for amplifying nucleic acids to detect the T to C substitution at position 6 in the donor splice site of intron 20 and the G to C transversion in exon 19 (see page 12, col. 1).

Slaugenhaupt does not teach packaging primers for detecting these mutations, and particularly primers consisting of present SEQ ID NO: 6-9, in kits.

However, Slaugenhaupt does teach the genomic sequence of the IKAP gene (see Figure 6 therein) and teaches that the cDNA for this sequence was known in the art at the time the invention was made (see page 10). Given the disclosure of Slaugenhaupt of the location of the 2 mutations within the IKAP gene, the disclosure of the genomic and cDNA sequences flanking the 2 mutations, and the disclosure of the use of PCR primers to amplify nucleic acid sequences containing the 2 mutations, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have generated additional primers, including the primers of present SEQ ID NO: 6-9, in order to have facilitated the detection of the intron 20 splice site and exon 19 mutations. Designing primers which are equivalents to those taught in the art is routine experimentation. The parameters and objectives involved in the selection of primers were well known in the art at the time the invention was made. Moreover, software programs were readily available which aid in the identification of conserved and variable sequences and in the selection of optimum primer pairs. The prior art is replete with guidance and information necessary to permit the ordinary artisan to design additional primers for the amplification of IKAP sequences containing the FD associated mutations

in the intron 20 splice site and exon 19. As discussed above, the ordinary artisan would have been motivated to have designed additional primers for amplifying IKAP sequences so as to have provided additional primers which could be used to amplify and detect the FD mutations in the intron 20 splice site and exon 19. Further, the ordinary artisan would have had more than a reasonable expectation of success of obtaining additional primers for amplifying IKAP sequences. Thus, for the reasons provided above, and in the absence of evidence to the contrary, the primers of present SEQ ID NO: 6-9 for detecting the FD mutations in intron 20 and exon 19 would have been obvious to one of ordinary skill in the art.

Further, reagent kits for performing DNA detection assays were conventional in the field of molecular biology at the time the invention was made. In particular, Ahren discloses the general concept of kits for performing nucleic acid detection methods and discloses that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay and allows investigators to save time and money (see for example page 23).

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged primers for amplifying the IKAP sequences containing the intron 20 splice site mutation and exon 19 mutation, and particularly primers consisting of SEQ ID NO: 6-9, in a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art wishing to amplify IKAP

sequences and detect the presence of the intron 20 splice site and exon 19 mutations associated with FD.

**Response to remarks:**

In the response, Applicants state that the rejection based on the '299 application as the primary reference can no longer stand. To the extent that this argument applies to the present grounds of rejection, it is noted that the Slaugenhaupt (US 2002/0169299) publication does in fact claim nucleic acids and the present claims are obvious over the claimed subject matter of the '299 publication. Accordingly, as discussed in paragraph 3 above, a 131 declaration may not be used to overcome a rejection based on a publication claiming the same patentable invention to which the present claims are directed. Thereby, the rejection is maintained for the reasons stated above.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Carla Myers/

Primary Examiner, Art Unit 1634